MATHEMATICAL MODEL AND EXPERIMENTAL VALIDATION OF LOCAL DELIVERY OF PAMIDRONATE TO BONE ADJACENT TO PAMIDRONATE - PMMA BONE CEMENT

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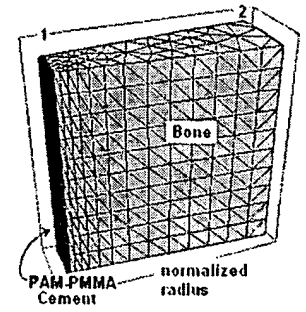
BACKGROUND: Cemented orthopaedic joints undergo time dependent aseptic loosening that is the culmination of events that begin with the formation of wear debris by the articulating joint components that induces macrophage infiltration and osteoclastic bone resorption. We have developed a PMMA cement blended with the bisphosphonate pamidronate (PAM) to inhibit the osteoclast activity. The cement serves as a prosthetic grout and local depot to deliver PAM to periprosthetic bone. A distributed parameter mathematical model was developed to facilitate studies investigating the drug delivery characteristics of PAM-PMMA cement formulations and estimating PAM distribution profiles throughout bone adjacent to PAM-PMMA cement. Herein we present the model and results from simulations to estimate the radial distribution of PAM in canine femur harvested one year following hip replacement using PAM-PMMA cement. **METHOD:** The elution and transport phenomena of PAM from the polymerized PMMA matrix across the periprosthetic gap to the hydroxyapatite binding sites within bone can be modeled using the coupled "diffusion-dispersion-reaction" partial differential equations shown below:

$$\nabla\cdot(D\cdot\nabla P)-f_v\cdot\nabla P-K_{ca}*P*SV_{ratio}*(W_{max}-W)=\varepsilon*\partial P/\partial t \quad [I]$$

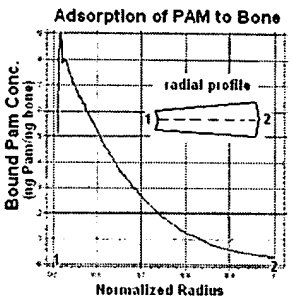
[1] [2] [3] [4]

$$K_{ca}*P*SV_{ratio}*(W_{max}-W)/((1-\varepsilon)*\rho_O)=\partial W/\partial t \quad [II]$$

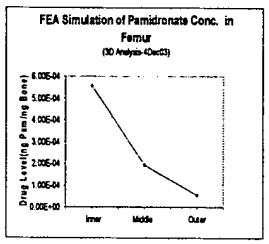
Equation **[I]** is a macroscopic material balance for the PAM eluting from the PMMA matrix and moving through the adjacent bone. Term [1] is a diffusion expression describing the passive component of free PAM movement throughout the open pore structure of bone; [2] is the dispersion expression that describes the convective component of free PAM movement; [3] is the binding term that describes the rate of PAM adsorption onto the bone's hydroxyapatite sites and accounts for the removal of PAM from the fluid stream. It is written to reflect Langmuir adsorption kinetics, the binding mode recommended to determine the affinity of bisphosphonates on bone (1). Term [4] is the rate of change for PAM in intra-osseous fluid. Equation **[II]** describes the adsorption of PAM onto bone from the intra-osseous fluid moving through the open pore bone matrix. Two simplifying assumptions are used in this model: 1. All parameters are time, concentration and position invariant, and 2. No desorption term is required because PAM binds irreversibly to bone. The equation parameters are defined as follows: **P** is the free PAM (gram drug/cc bone); **W** and $\mathbf{W_{max}}$ are the bound and maximum amount of PAM that can bind to bone (grm drug/grm bone), respectively; $\mathbf{K_{ca}}$ is the adsorption binding rate (hr^{-1}); **D** is a diffusion coefficient for PAM through intra-osseous fluids(cm^2/hr); f_v is the intra-osseous radial fluid velocity (cm/hr); $\mathbf{SV_{ratio}}$ is the surface to volume ratio for bone (cm^{-1}); ρ_o is bone density (grm/cm^3); ε is the bone porosity ratio; and **t** is time (hr). Published values for the material parameters $\mathbf{SV_{ratio}}$, ρ_o and ε for canine bone were used, however no published values for the reaction–diffusion-velocity parameters $\mathbf{W_{max}}$, $\mathbf{K_{ca}}$, **D**, or f_v within bone following cemented joint replacement were identified. An estimation algorithm was developed to determine suitable values for these parameters. Briefly, the parameters were varied until the computed PAM radial distribution matched the HPLC measurements of PAM within the diaphyseal segment of the canine femur. Constraints were imposed to ensure that parameter values remained within reasonable physiological ranges. A cylindrical annular wedge was used to model the femur and cement mantle. The data from a 456 hour elution study of PAM from PAM-PMMA polymerized cement was used to create an input function that was applied to the cement end of the wedge. All simulations were performed using FlexPDE v4.06b, a partial differential equation solver, and Microsoft Excel. **RESULTS:** Figures A-E present the simulation results after a 1000-hour simulation period; profiles shown in Figs. B and E were achieved by ~550 hours. Fig. A is the cylindrical geometry used to model the canine femur; Fig. B is the predicted radial concentration profile of bound PAM within the bone; Fig. C presents the radial concentration profile of PAM derived using Excel with FlexPDE data segmented into three parts to approximate the HPLC radial profile results shown in Fig. D. Fig. E is the distribution profile of free PAM throughout the bone; this quantity is negligible.



A



B



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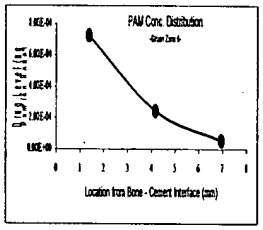
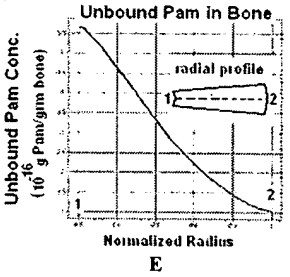


D



E

Parameter	Value
D	3.0E-5 cm^2/hr
K_{ca}	0.09 hr^{-1}
W_{max}	0.002 grm PAM/grm bone
f_v	0.001 cm/hr
ε	0.1 (Calc. Tiss. Int. 36:S72-6, 1984)
ρ_o	2.0 (Calc. Tiss. Int. 34:332-6, 1982)
SV_{ratio}	54 (Radiation Research 120:83-101, 1989)

Table 1

Table 1 presents the values of the parameters used to generate the findings shown in Figs. B, C, and E. The computed estimates for $\mathbf{W_{max}}$, $\mathbf{K_{ca}}$, **D**, or f_v using the Fig. D data are listed first, and then the published values for parameters $\mathbf{SV_{ratio}}$, ρ_o and ε along with their literature citation. **DISCUSSION:** The computed radial distribution shown in Fig. C closely approximates the HPLC data presented in Fig. D, a finding that supports the use of the proposed model. From Table 1 we observe that $\mathbf{K_{ca}}$ for PAM is similar to that for Ga^{+3} {0.08 hr^{-1}} (2), an antiresorptive agent, however $\mathbf{W_{max}}$ for PAM estimated from this analysis, 5.41e-6 moles PAM/grm bone, is 13X lower than that reported for Ga^{+3} {7.15e-5 moles Ga^{+3}/grm bone} (2). Further, the $\mathbf{W_{max}}$ value suggests that the concentration of PAM within the inner cortex was approaching saturation with the PAM-PMMA formulation used in the arthroplasty. **D** is 3.2X larger than that reported for Gentamicin {9.3e-6 cm^2/hr} (3), an antibiotic formulated with PMMA, a reasonable finding since PAM is a smaller molecule and the parameter probably includes a convective component. The radial velocity, f_v, was 0.001 cm/hr, significantly lower than normal average bone blood velocity [1.4-7.2 cm/hr] (4), suggesting that radial fluid movement was compromised by the arthroplasty. This parameter is also the most sensitive parameter in the model, i.e. the radial distribution profile is dramatically altered as its value is increased.

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